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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
05/10/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/599,588	BJURSELL ET AL.	
	Examiner	Art Unit	
	ZACHARY HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6 and 8-21* is/are pending in the application.

4a) Of the above claim(s) *3,5,6,8,9,11-15 and 18-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,10,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-6 and 8-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 October 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/8/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The set of claims filed on 2/22/11 has been entered in full. No changes are made to the immediate previous set of claims filed on 3/9/10.

Claim 10 is listed with the status as "New"; however, this claim was previously presented in the set of claims filed on 3/9/10 and entered in the Office Action mailed on 9/28/10. Therefore, the correct status listing for claim 10 should be "(Previously presented)". The 2/22/11 set of claims has been entered despite this incorrect status identifier. Applicants should correct this status identifier in any future claim listings.

Claims 1, 3-6 and 8-21 are pending in the instant application.

Election/Restrictions

Claims 3, 5, 6, 8 and 9 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the 7/27/09 reply.

Two elections of species were required in the Office Action mailed 9/28/10. Applicants' elections with traverse of (1) LOX-1 as the species of receptor and (2) "measuring binding of CEL to cells expressing the receptor" as the species of means of measuring receptor binding in the 11/23/10 reply are acknowledged.

The traversal of species election (1) is on the grounds that the "receptors share a unifying feature" in that all of the species "can be bound by CEL when acting as a bridging molecule", and therefore "must all possess a common structural element" that is a "CEL binding site" and which provides a common utility based on a common structural feature.

This is not found persuasive because while the specification asserts that each of the receptor species can bind CEL and promote atherogenesis, the specification does not provide any evidence of such. Furthermore, even if multiple receptor species can bind to CEL and promote atherogenesis, this does not indicate that each receptor species binds to CEL via an identical structure, or binds to the identical region of CEL.

The different polypeptide structure of each receptor suggests that each would not bind an identical structure on CEL, and the specification provides no evidence to the contrary. Furthermore, the asserted technical feature cannot constitute a special technical feature as defined by PCT rule 13.2 because the prior art teaches that LOX-1 binds to CEL (see the rejection under 35 USC § 102(b) set forth below), and thus the asserted technical feature does not define a contribution over the prior art.

The traversal of species election (2) is on the grounds that the claimed "means of measuring receptor are unitary" because they possess a common utility in establishing the extent of binding of CEL to a receptor. Applicants cite PCT Rule 13.2 and argue that while it requires the presence of a special technical feature, it does not require an identical common structure.

This is not found persuasive because while a common structure is not required *per se* to establish a special technical structure, the lack of a common utility based on a common structure can provide evidence in support of a lack of a special technical feature among species. Applicants point to 13.2 as stating that a special technical feature only requires a contribution which the species as a whole makes over the prior art, yet Applicants do not point out any contribution as a whole made over the prior art made by claimed species of measuring binding. A means of measuring CEL binding to a receptor expressed by a cell is taught by the prior art, as evidenced by the rejection under 35 USC § 102(b) set forth below. Therefore, it is maintained that the species do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 1.32, the species lack the same or corresponding special technical feature.

Claims 11-15 and 18-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 4, 10, 16 and 17 are under consideration, as they read upon the elected species.

Information Disclosure Statement

The Information Disclosure Statement of 3/8/10 has been considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the 10/15/09 Office Action.

As noted at page 2 of the restriction requirement mailed 9/28/10, Applicants' response filed on 7/14/10 to the Notice to Comply with Sequence Listing Requirements under 37 CFR § 1.821 mailed on 10/15/09 was found sufficient and the requirements set forth at pg 2-3 of the 10/15/09 Office Action are *withdrawn.*

The objections to the specification at pg 3 are *withdrawn* in view of Applicants' amendments to the specification filed on 3/9/10.

All objections and/or rejections of claim 2 are moot in view of Applicants' cancellation of this claim.

The objection to claims 1 and 4 at pg 4 is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 4 under 35 U.S.C § 112, second paragraph, at pg 4-5 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claim 1 under 35 U.S.C. § 102(b) at pg 11-12 as being anticipated by Lange et al (EP 0650620) is *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. This objection was set forth at pg 3-4 of the 10/15/09 Office Action.

To reiterate, Applicants submitted a declaration on 4/16/08 that is defective because non-initialed and non-dated alterations have been made. See 37 CFR 1.52(c). The addresses of the Applicants Karl Bjursell and Jeanette Nilsson were altered without

including a corresponding set of initials and date. The execution of the declaration by said Applicants is not sufficient to meet this requirement. See MPEP 605.04(a).

It is noted that this objection can be overcome by filing a corrected declaration or by filing an application data sheet (ADS) including the addresses of the Applicants.

In the 3/9/10 response, Applicants state that they "are providing a newly execute Oath & Declaration herewith" (pg 8).

Applicants' arguments have been fully considered but are not found persuasive. While Applicants indicated an intention to file a new Oath or Declaration, no such document was received with the response filed on 3/9/10 or subsequently. As such, the objection is maintained.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 10, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was set forth at pg 5-9 of the 10/15/09 Office Action for claims 1 and 4; new claims 10, 16 and 17 depend from claim 1 and are herewith added to the rejection.

Applicants have deleted the recited intended use for the identified compound ("useful for prevention and treatment of atherosclerosis") from independent claim 1, but the instant specification does not teach any other use for a compound identified to decrease binding of CEL to the receptors now recited in the claim (including the elected species of LOX-1, which is a scavenger receptor); therefore, the rejection of the claims for failing to enable such a use is maintained for the reasons of record.

Applicants' arguments (3/19/10; pg 13-16) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that "it is clear that CEL can have a role in promoting atherogenesis by virtue of its ability to act as a "bridging molecule" between vascular endothelial receptor and plasma-borne atherogenic lipoprotein components, as discussed above" (pg 13), referring to the "Overview of the Invention" (pg 8-12), which includes three sections. The first is a review of atherogenesis ("Atherogenesis"; pg 8-9)" that teaches that "bridging molecules" promote atherogenesis by facilitating the interaction between "cellular components of the vascular endothelium and atherogenic lipoprotein components from the plasma" (pg 9). The second section ("Art-Known Mechanisms of Atherogenic Lipoproteins"; pg 9-10)" describes LPL (lipoprotein lipase) as one such bridging molecule, pointing to Gustafsson et al (2004; reference C21 on the 5/22/09 IDS) and Pentikainen et al (2002; reference C26 on the 5/22/09 IDS) in support. The third section ("The Present Invention"; pg 10-12) argues that CEL is also such a bridging molecule based on its ability to bind "to both endothelial and plasma-derived atherogenic lipoprotein factors". Applicants point to Figure 5B and 5C as demonstrating that CEL associated with HDL/LDL-fractions in the plasma and thus "can bind to atherogenic lipoproteins (that is, high and low density lipoproteins) present in the plasma" (pg 11). Applicants further argue that "as discussed at page 16, lines 1-2 of the present application, CEL can associate with apoB, which is the protein component of lipoproteins within the plasma". Applicants further argue that "as discussed at page 17, lines 11-12 ... the N-terminal part of CEL binds to avidly to heparin and several of its variants, which are key structures in proteoglycans found on the surface of vascular endothelium" (pg 11). Applicants further argue that "as discussed at page 17, lines 14 ... CEL can bind to the scavenger receptor LOX-1 which is clearly a component of vascular endothelial cells"; Applicants point to Moriwaki et al (1998; reference C15 on the 3/21/07 IDS) (pg 11). Applicants further argue that "CEL present in lipoprotein particles has the potential to act as a bridging molecule by binding to other receptors, as claimed"; Applicants point to Camarota et al (June 2004; reference C9 on the 3/21/07 IDS); Rebai et al 2005 (reference C16 on the 3/21/07 IDS); McKillop et al (Jan 2004;

reference C24 on the 5/22/09 IDS), and Kodvawala et al (2005; reference C23 on the 5/22/09 IDS) which "shows that atherosclerosis is promoted by expression of CEL in mouse macrophages (ordinarily mouse macrophages do not express CEL)" (pg 12 and paragraph bridging pages 13-14)

Applicants' arguments have been fully considered but are not found persuasive. The hypothesis that CEL is a "bridging molecule" that contributes to retention of atherogenic lipoproteins in atherosclerosis was considered as part of the rejection set forth previously. The teachings of Gustafsson et al (2004) and Pentikainen et al (2002) have been fully considered but are not sufficient to overcome the rejection. These references do not provide any evidence that is specific to CEL. Gustafsson et al instead teach, "[a]therosclerosis is a multifactorial disease whose pathogenesis unclear" (Abstract), underscoring that the instant specification must teach the skilled artisan a specific role of CEL in the pathogenesis of atherosclerosis if it is to be used to identify compounds for treatment of such. As set forth previously, the teachings of the instant specification are not sufficient to demonstrate that CEL contributes to retention of atherogenic lipoproteins in atherosclerosis. Figures 5B and 5C were considered previously as part of the teachings of Example 1, which teaches that "amount of CEL appeared to a certain extent correlated to the amount of apoB" in HDL/LDL fractions of serum from donors with high chylomicron content (¶ 86). These reported results are not disputed, but do not indicate whether the amount of CEL is a cause or symptom of high chylomicron content, and do not demonstrate a role of CEL in causing atherogenesis, or provide a receptor to which it binds in promoting atherogenesis. Applicants argue that the specification at page 16, lines 1-2 shows that CEL can associate with apoB, but that portion of the specification only teaches that "CEL and apoB staining appear in the same regions of the atherosclerotic carotid artery", i.e., co-expression in the same tissue, rather than any binding between CEL and apoB. While the N-terminal region of CEL can bind to heparin and several heparin variants, the specification does not demonstrate any role for such binding in promoting atherogenesis, and in fact teaches that "[t]he binding of CEL to vascular proteoglycans remains to be thoroughly investigated", underscoring the need for further research to determine such. Likewise,

the prior art (Bruneau et al, 2003; see the 102(b) rejection below) and specification teach that CEL can bind to the scavenger receptor LOX-1 as part of transport across intestinal enterocytes, but the specification does not demonstrate any role of such binding in promoting atherogenesis. The specification cites Moriwaki et al (1998) as teaching that LOX-1 is a receptor for oxidized LDL (ox-LDL) in macrophages, but does not provide any evidence that LOX-1 which binds ox-LDL also binds CEL to promote atherogenesis. The specification instead teaches that these results provide "another possible clue to why and how CEL accumulates in the vascular wall" (pg 17), underscoring the need for further research to determine whether binding of CEL to LOX-1 actually occurs in vascular tissue and contributes to atherogenesis. The teachings of Camarota et al (June 2004), Rebai et al (2005), and Kodvawala et al (2005) were published after the claimed priority date for the instant application (4/2/04), and thus cannot provide evidence of what was known to the skilled artisan at that time. Further, Camarota et al, Rebais et al, and Mckillop do not demonstrate any role of CEL in promoting atherogenesis; Camarota et al instead provide results suggesting a role for CEL in hepatic selective uptake and metabolism of HDL cholesteryl esters (see Abstract), and teach that mice lacking CEL have elevated plasma cholesterol (pg 27605). Rebais et al instead provide *in vitro* results suggesting a role for CEL in promoting angiogenesis. McKillop et al, while published before the claimed priority date, teach only that "the function of oligosaccharides on BSSL may be important in mediating an adhesive activity in cell-cell recognition and for the behaviour and activity of the enzyme in the intestine" (pg 15). While Kodvawala et al teach that "CEL expression in macrophages is pro-atherogenic and that the mechanism is because of its hydrolysis of ceramide and lysophophatidylcholine in promoting cholesterol esterification and decreasing cholesterol efflux" (see Abstract, page 38592), Kodvawala et al do not teach any specific receptor(s) that bind to CEL to promote retention of atherogenic lipoproteins (e.g., LDL). There is no teaching in Kodvawala et al suggesting that CEL is acting as a bridging molecule that binds a receptor in promoting atherogenesis.

Applicants further argue that the genus of receptors encompassed by the claims has been narrowed to "specific types of receptors which are reasonably understood to play a role in the mechanism of endothelial retention of atherogenic lipoproteins which underlie the development of atherosclerotic lesions" (pg 14) and this renders moot the issue of the claims encompassing a "vast and varied genus" of receptors.

Applicants' arguments have been fully considered but are not found persuasive. While the claims have been narrowed from a method that uses any type of receptor, the claims still encompass a method of using a receptor that is any type of vascular proteoglycan, scavenger receptor (including the elected species of LOX-1), AGE receptor, lipoprotein lipase, apolipoprotein, lipoprotein or lipoprotein particle. It remains that, even assuming that CEL is a cause of atherosclerotic lesions, the specification fails to identify any specific receptor that promotes atherosclerosis through interaction with CEL. Applicants' response does not provide any evidence of such a receptor. Enabling a use for the claimed method requires that the modulation of binding of CEL to a receptor is an indication of whether a compound can be used for prevention and treatment of atherosclerosis or reducing the retention of atherogenic lipoproteins in atherogenesis. However, instead of enabling the skilled artisan to practice the claimed method by providing an interaction between CEL and a specific receptor that promotes atherosclerosis, the specification simply advances a vast and varied genus of "suitable receptors" including proteoglycans such as glycosaminoglycans, heparin, heparan sulphate, chondroitin-6-sulphate, chondroitin-4-sulphate, dermatan sulphate; scavenger receptors such as SR-A types I, II and III, MARCO, SR-BI, CD36, SR-C1, SR-D, Macrosialin/ CD86, SR-E, LOX-1 (lectin-like ox-LDL receptor), SR-F, SREC-1, SR-PSOX, FEEL-1, FEEL-2; AGE receptors such as RAGE, 80K-H, OST 48, Galectin-3 ... LPL (lipoprotein lipase); apolipoproteins such as apo A-I, apo A-II, apo B-100, apo B-48, apo C-I, apo C-II, apo C-III, apo E; lipoproteins and lipoprotein particles such as the VLDLs (very low-density lipoproteins) VLDL1, VLDL2 and VLDL3, the IDLs (intermediate-density lipoproteins) IDL1, IDL2 and IDL3, LDLs (low density lipoproteins) LDL1, LDL2 and LDL3, the HDLs (high-density lipoproteins) preβ-HDL, α-HDL, HDL1, HDL2, and HDL3 ... as well as chylomicrons". While CEL may bind one or more of these

compounds (e.g., the prior art teaches binding of CEL to LOX-1), the specification fails to teach which, if any of these compounds, binds CEL as part of the atherogenic process, such that modulating the interaction would result in treatment of atherosclerosis and/or reducing the retention of atherogenic lipoproteins. The specification merely invites the skilled artisan to engage in further experimentation to determine the nature of any receptor (if any) that binds CEL such that the interaction is involved in the process of atherosclerosis.

Applicants further argue that Bengtsson-Ellmark et al (2004; reference C20 on the 5/22/09 IDS), which was cited in the rejection set forth previously, provide teachings only regarding the enzymatic role of CEL rather than structural role of CEL.

Applicants' arguments have been fully considered but are not found persuasive. The statement by Bengstrom-Ellmark et al that "is largely unknown to what extent but is largely unknown to what extent CEL could be involved in determining the serum lipid levels" (Abstract and page 628) relates to any role of CEL. Nowhere else do Bengstrom-Ellmark et al indicate that the structural (rather than enzymatic) role of CEL in serum lipids or atherosclerosis is known. Bengtsson-Ellmark et al (2004) was published after the earliest date to which the instant application claims priority, therefore it is maintained that this reference provides evidence that the skilled artisan could not predict what the role of CEL in atherogenesis was at the time of filing of the instant application.

Applicants further argue that the specification does not need to teach "one or more procedures to measure the ability of the test compound to reduce the retention of atherogenic lipoproteins" as recited in claim 4, because "methods of assessing the retention of atherogenic lipoproteins in the extracellular cell matrix (ECM) were well known in the art at the priority date of the application (2 April 2004)"; in support of this argument, Applicants point to Auerbach et al, 1999; Olin-Lewis et al, 2002; and Skalen et al 2002 (each reference cited on the 3/8/10 IDS). Applicants further argue the statement in the rejection that "it is not clear how such a procedure could be designed in the absence of a specific molecule that CEL binds to" by stating that the receptors to which CEL binds have been identified in the claims, which allows the skilled artisan to

appreciate which interactions must be disrupted in order to reduce the retention of atherogenic lipoproteins caused by CEL (pg 16).

Applicants' arguments have been fully considered but are not found persuasive. The teachings of Auerbach et al, 1999; Olin-Lewis et al, 2002; and Skalen et al 2002 have been fully considered but are not sufficient to overcome the rejection. In the arguments, Applicants refer to methods of "assessing the retention of atherogenic lipoproteins in the extracellular cell matrix (ECM)", yet claim 4 and specification are directed generally to "measuring the ability of a test compound ... to reduce the retention of atherogenic lipoproteins". Claim 4 and the instant specification do not refer to measuring the retention of lipoproteins in the ECM. Thus, Applicants' arguments are directed to only one embodiment encompassed by the claim, but not generally to that which is recited in the claim. Furthermore, the teachings of Auerbach et al pointed to by Applicants are directed solely to an assay that measures the effect of lipoprotein lipase on lipoprotein(a) (Lp(a)) binding to the ECM, and the teachings of Olin-Lewis et al are directed solely to binding of HDL to the ECM. The instant specification does not identify Lp(a) (lipoprotein A) or HDL as "atherogenic lipoproteins" as recited in the claims. The instant specification does not provide any teachings regarding Lp(a). The instant specification contains a few references to HDL, but does not identify it as a "atherogenic lipoprotein", or indicate that CEL can reduce retention of HDL in the ECM or elsewhere. The only atherogenic lipoprotein identified in the specification is LDL (¶ 5 of the published application). Thus, there is nothing that would lead the skilled artisan from the limited teachings in the instant specification regarding the measuring the ability of a test compound to reduce retention of atherogenic lipoproteins to the specific teachings of Auerbach et al or Olin-Lewis et al. Skalen et al describe an experiment measuring the subendothelial retention of mutant LDL as compared to control LDL. However, Skalen et al present this as a novel experiment demonstrating the ability of proteoglycan to modulate retention of LDL rather an established assay to use for screening molecules to determine the ability to reduce retention of atherogenic lipoproteins. Skalen et al do not use the assay to screen for compounds that reduce the retention of LDL. There is nothing in the instant specification pointing to the use of Skalen et al, and the novelty of

the findings of Skalen et al do not suggest its use as a standard technique. Skalen et al further teach, "[m]ouse LDL often contain apoE, but apoB100 is the sole apolipoprotein of human LDL. Thus, bridging molecules are probably less important than a direct interaction between apoB100 and proteoglycans for subendothelial retention of atherogenic lipoproteins in humans", further indicating that the skilled artisan would not regard the experiments described in Skalen et al as routine assays for use in screening compounds.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1, 4, 10, 16 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth at pg 9-11 of the 10/15/09 Office Action for claims 1 and 4; new claims 10, 16 and 17 depend from claim 1 and are herewith added to the rejection.

Applicants' arguments (3/9/10; pg 16-17) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the claims have been narrowed "to define specific categories of receptors" that are "present on the vascular endothelium or are plasma borne components of atherogenic lipoproteins" and CEL can act as a "bridging molecule" to bind both types and "bring about the subendothelial retention of atherogenic lipoproteins", promoting atherogenesis (pg 16). Applicants argue that because the receptors to which CEL binds are identified in the claims and the specification at page 7, lines 3-14, and have a well-defined role in atherogenesis, the claimed subject matter was described in the specification "in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention". Applicants further argue that it is not necessary to describe specific methods to determine whether a test

compound can reduce the retention of atherogenic lipoproteins as such methods were available to the skilled artisan as described above.

Applicants' arguments have been fully considered but are not found persuasive. While the claims have been narrowed from a method of using any type of receptor, the claims still encompass a method of using a receptor that is any type of vascular proteoglycan, scavenger receptor (including the elected species of LOX-1), AGE receptor, lipoprotein lipase, apolipoprotein, lipoprotein or lipoprotein particle. It remains that, even assuming that CEL is a cause of atherosclerotic lesions, the specification fails to describe any specific receptor that promotes atherosclerosis through interaction with CEL. Applicants' response does not provide any evidence of such a receptor. Written description for the claimed method requires that the modulation of binding of CEL to a receptor is an indication of whether a compound can be used for prevention and treatment of atherosclerosis or reducing the retention of atherogenic lipoproteins in atherogenesis, which are the only disclosed uses for the claimed method. However, instead of describing an interaction between CEL and a specific receptor that promotes atherosclerosis, the specification simply advances a vast and varied genus of "suitable receptors" including proteoglycans such as glycosaminoglycans, heparin, heparan sulphate, chondroitin-6-sulphate, chondroitin-4-sulphate, dermatan sulphate; scavenger receptors such as SR-A types I, II and III, MARCO, SR-BI, CD36, SR-C1, SR-D, Macrosialin/ CD86, SR-E, LOX-1 (lectin-like ox-LDL receptor), SR-F, SREC-1, SR-PSOX, FEEL-1, FEEL-2; AGE receptors such as RAGE, 80K-H, OST 48, Galectin-3 … LPL (lipoprotein lipase); apolipoproteins such as apo A-I, apo A-II, apo B-100, apo B-48, apo C-I, apo C-II, apo C-III, apo E; lipoproteins and lipoprotein particles such as the VLDLs (very low-density lipoproteins) VLDL1, VLDL2 and VLDL3, the IDLs (intermediate-density lipoproteins) IDL1, IDL2 and IDL3, LDLs (low density lipoproteins) LDL1, LDL2 and LDL3, the HDLs (high-density lipoproteins) preβ-HDL, α-HDL, HDL1, HDL2, and HDL3 ... as well as chylomicrons". While CEL may bind one or more of these compounds (e.g., the prior art teaches binding of CEL to heparin), the specification fails to describe which, if any of these compounds, binds CEL as part of the atherogenic process, such that modulating the interaction would result in treatment of

atherosclerosis and/or reducing the retention of atherogenic lipoproteins. Thus, it is maintained the specification fails to provide possession of "a receptor" to which CEL binds as recited in the claims, and the claimed method lacks written description. It is also maintained that claim 4 additionally lacks written description because the specification fails to describe "one or more procedure to measure the ability of the test compound to reduce the retention of atherogenic lipoproteins". No specific procedures of this type (either *in vitro* or *in vivo*) are described and it is not clear how such a procedure could be designed in absence of a specific molecule that CEL binds to as part of promotion of retention of atherogenic lipoproteins. As such, the specification does not provide sufficient description for the skilled artisan to possess such procedures. Applicants' arguments regarding this portion of the rejection are addressed above in the section titled "Claim Rejections - 35 USC § 112, first paragraph - enablement".

New rejections necessitated by Applicants' amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruneau et al (2003. Molecular Biology of the Cell. 14: 2861-2875; reference C5 on the 3/21/07 IDS).

As amended, claims 1 and 10 each encompass a method comprising assaying a compound for its ability to decrease the binding ability of carboxyl ester lipase (CEL) to a receptor that is the scavenger receptor LOX-1 (lectin-like ox-LDL receptor). Applicants have deleted the intended use for the compounds ("for prevention and treatment of atherosclerosis") from the preamble of the claims (however, it is noted this intended use was not given patentable weight to distinguish the claimed method from the prior art).

Bruneau et al teach that CEL (also known as bile sale-dependent lipase or BSDL) binds to LOX-1 expressed on the surface of INT-407 Intestinal Cells as part of transcytosis (see Title, Abstract and Introduction on page 2861). Bruneau et al show that a monoclonal antibody to CEL known as mAbJ28 results in reduced transcytosis of CEL through INT-407 cells (see Figure 3 on page 2866). Thus, Bruneau et al teach a method comprising assaying a compound (mAbJ28) for its ability to decrease the binding ability of CEL to LOX-1. Therefore, the teachings of Bruneau et al anticipate claims 1 and 10.

New claim 16 depends from claim 1 and limits the method to one wherein the assaying comprises measuring receptor binding of CEL to cells expressing the receptor on their surface. In the teachings of Bruneau et al described above, the INT-407 cells expressed LOX-1 on the cell surface, as shown by Figure 5A on page 2868. Therefore, the teachings of Bruneau et al also anticipate claim 16.

New claim 17 depends from claim 16 and limits the method to one wherein the assaying comprises measuring binding of labeled CEL. The instant specification does not provide a limiting definition of the term "labeled"; instead the instant specification only provides examples of such (¶ 32 of the published application). As such, the term "label" is interpreted broadly to include natural moieties that can be recognized. Bruneau et al further teach that mAbJ28 binds to "the fucosylated J28 epitope of BSDL" (pg 2862). Thus, fucosylated BSDL is encompassed by the term "labeled CEL" as used in claim 17. Therefore, in the teachings of Bruneau et al described above, the binding of labeled CEL (i.e., fucosylated CEL aka BSDL) to LOX-1 is measured. Therefore, the teachings of Bruneau et al also anticipate claim 17.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647